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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/779,376	FAN ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2007* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9-16,19-23,26 and 30-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9-16,19-23,26 and 30-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *14 November 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/2007* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office communication filed on January 11, 2007 has been entered. The claims pending in this application are claims 5, 9-16, 19-23, 26, and 30-64. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on December 20, 2006.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 5, 13, 32, 39, 45, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (US Patent No. 6, 534,293, priority date: January 6, 1999) in view of Schnelder *et al.,* (US Patent No. 4,882,269, published on November 21, 1989).

Barany *et al.,* teach detection of nucleic acid sequence differences using coupled ligase detection and polymerase chain reactions.

Regarding claims 5, 32, 39, and 57, Barany *et al.,*, teach that a first oligonucleotide probe having a target-specific portion, addressable array-specific portion and a upstream primer-specific portion, and a second oligonucleotide probe having a target-specific portion, a downstream primer-specific portion, and a detectable label are hybridized adjacent to one another on a corresponding target nucleotide sequence and are ligated together in a ligase chain reaction. However, if there is a mismatch in ligation end of the first or second probe, this mismatch will interfere with such ligation. Then unligated the first probe and the second probe are removed and PCR-amplify the ligation product sequence (in the second probe) wherein one primer has a detectable reporter label. Finally, PCR products are hybridized with a DNA array by the addressable array-specific portions of the PCR products (from the first oligonucleotide from Barany *et al.,*) wherein the array has different capture oligonucleotides immobilized at different particular sites and have nucleotide sequences complementary to the addressable array-specific portions of the PCR products, and the labels of the PCR products captured on the DNA array at particular sites are detected as recited in steps f) and g) of claims 5, 32, 39, and 57 (see Figure 60, and column 80, claim 1 in columns 157 and 158). Note that: (1) the specification defines "universal priming site" as " a sequence of the probe that will bind a PCR primer for amplification" (see page 13, lines 14 and 15), the first probe and second probe taught by Barany *et al.,* are considered as first probe with the first, second, fifth portions, and second ligation probe with the third and fourth portions as recited in claims 5, 32, 39, and 57; (2) as shown in Figure

60, base C in left probe (a first ligation probe) is considered as a first base at an interrogation position as recited in claim 5 and 39 or an interrogation position that is complementary to said detection position in a first ligation probe as recited in claim 32 and 57; and (4) according to the definition of "adaptor sequence" (see the specification, page 19, third paragraph), the fifth portion of the first ligation probe is considered to have an exogenous adaptor sequence as recited in claims 39 and 57 because the second ligation probe is synthesized *in vitro* and artificially made, and is exogenous to the target sequence.

Regarding claims 13 and 45, since Barany *et al.*, teach to amplify the ligation product by PCR and claims 13 and 45 are directed to basic PCR steps include repeated denaturation, annealing and extension, Barany *et al.*, disclose claims 13 and 45.

Barany *et al.*, do not disclose immobilizing said ligation complex (a hybridization complex formed by a target sequence, a first ligation probe, and a second ligation probe) to a solid support as recited in step c) of claims 5, 32, 39, and 57.

Schnelder *et al.*, teach immobilizing a hybridization complex formed in a solution to a solid support (see column 16, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 5, 32, 39, and 57 by immobilizing said ligation complex (a hybridization complex formed by a target sequence, a first ligation probe, and a second ligation probe) to a solid support in view of the patents of Barany *et al.*, and Schnelder *et al.*. One having ordinary skill in the art would have been motivated to do so because immobilizing a hybridization complex formed in a solution to a

solid support would enhance separation of the hybridization complex from unhybridized probes and, comparing with a hybridization assay in solution, the signal generated from immobilized hybridization complexes would be detected directly from the solid support and would be readily be read and quantified (see column 16, lines 40-52). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to immobilize said ligation complex (a hybridization complex formed by a target sequence, a first ligation probe, and a second ligation probe) to a solid support as recited in claims 5, 32, 39, and 57.

4. Claims 14-16, 34, 46-48, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Schnelder *et al.,* as applied to claims 5, 13, 32, 39, 45, and 57 above, and further in view of Walt *et al.,* (US Patent No. 6,327,410 B1, filed on September 11, 1998).

The teachings of Barany *et al.,* and Schnelder *et al.,* have been summarized previously, *supra.*

Barany *et al.,* and Schnelder *et al.,* do not disclose an array recited in claims 14-16, 34, 46-48, and 60.

Walt *et al.*, do teach an array comprising a substrate such as a fiber optical bundle recited in claims 16, 34, 48, and 60 with a patterned surface with discrete sites such as wells recited in claims 15 and 47, and a population of microspheres comprising at least a first subpopulation and a second subpopulation wherein said first subpopulation comprises a first nucleic acid and second subpopulation comprises a second nucleic acid, and wherein said microspheres are

randomly distributed on said surface such that said discrete sites contain microspheres recited in claims 14 and 46 (see Figures 7A and 7B, columns 3, 4, and 28-30).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 5 and 32 using an array recited in claims 14-16, 34, 46-48, and 60 in view of the patents of Barany *et al.*, Schnelder *et al.*, and Walt *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of nucleic acid array (ie., a regular oligonucleotide array taught by Barany *et al.*,) from another kind of nucleic acid array (an array with microspheres having immobilized nucleic acids taught by Walt *et al.*,) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement of one kind of nucleic acid array from another kind of nucleic acid array during the process of determining the identification of a nucleotide at a detection position in a target sequence would not change the method steps of the experiment since the array taught by Barany *et al.*, and the array taught by Walt *et al.*, are used for the same purpose (ie., a hybridization assay).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

5. Claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (US Patent No. 5,876,924, filed on July 31, 1996).

The teachings of Barany *et al.,* have been summarized previously, *supra.* As shown in above rejection, Barany *et al.,* teach claims 13 and 45.

Barany *et al.,* do not disclose step a) of claims 26, 33, 54, and 58, and claims 19-22, 31, 35, 42, 49-52, 59, and 61.

Regarding claims 10, 19-22, 26, 31, 33, 35, 42, 49-52, 54, 56, 58, 59, and 61, Zhang *et al.,* teach nucleic acid amplification method/hybridization signal amplification method. As shown in Figures 1 and 2, the two oligonucleotide probes (Capture/Amp-probe-1 and Amp-probe-2) are first hybridized adjacent to one another on a corresponding target nucleotide sequence of the target nucleic acid in a sample wherein the Capture/Amp-probe-1 is 3'-biotinylated. Then the complex comprising target nucleic acid-probes is separated from any unbound reactants using streptavidin-coated paramagnetic beads as recited in claims 10, 19, 20, 31, 42, 49, 50, and 56 and the probes is ligated together in a ligation chain reaction. Ligated product of Capture/Amp-probe-1 and Amp-probe-2 are used as a template for PCR (see Figures 1 and 2, and columns 10-17). This method is used to detect a single mutation in a target (see

column 6, first paragraph). Note that: (1) since claims 26, 33, 54, and 58 do not require that step a) must perform before step b), binding of target nucleic acid-probe complex to streptavidin-coated paramagnetic beads is considered to provide a support on which the target sequence is immobilized recited in step a) of claims 26, 33, 54, and 58; (2) Capture/Amp-probe-1 is considered to have a first portion and a second portion while AMP-PROBE-2 is considered to have third portion, fourth portion, and fifth portion (see attached Figure 1 with examiner's handwritings in the office action mailed on April 20, 2005) wherein said exogenous adapter sequence is nested between said third and fourth portions of said second ligation probe as recited in claim 59; (3) streptavidin-coated paramagnetic beads are considered as a double-stranded moiety as recited in claims 10 and 42 since they bind to and separate the complex comprising target nucleic acid-probes which is double stranded from any unbound reactants; (4) the target nucleic acid is considered to be indirectly immobilized on streptavidin-coated paramagnetic beads as recited in claims 19, 21, 49, and 51; (5) biotinylated Capture/Amp-probe-1 is considered as a functional attachment moiety recited in claims 22, 52, and 61 since this probe attaches the target nucleic acid to streptavidin-coated paramagnetic beads in the target nucleic acid-probe complex; and (6) a base located in 5' of capture/AMP-probe is considered as an interrogation position as recited in claims 26, 33, 54, and 58 (see Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61 in view of the patents of Barany *et al.*, and Zhang *et al.*. One having ordinary skill in the art would have been motivated to do so

because the simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.,*) from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.,*) in order to make hybridization probes (ie., a plurality of amplicons in step f) of claims 26, 33, 54, and 58) during the process for performing the methods recited in claims 26, 34, 54, and 58 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since LDR/PCR method of Zhang *et al.,* and LDR/PCR method of Barany *et al.,* are equivalent methods and are used for the same purpose (ie., producing hybridization probes).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

I. In page 19, last paragraph of applicant's remarks, applicant argues that "[T]he claimed invention expressly recites generating a plurality of amplicons where each amplicon contains a fifth portion having an adapter sequence that is distinct from the first, second, third and fourth portions of the claimed ligation probes. Because the fifth portion is distinct from other portions of the ligation probe it cannot specifically hybridize to the target sequence. Therefore, the

claimed ligation probes are distinct from the probes of Barany et al., which hybridize to the target sequence. The capture/amplification probe described by Zhang et al. also fails to describe specific hybridization with an adapter sequence because it uses ligand binding probes and because the alleged fifth portion is arbitrary and does not appear to hybridize to anything specific. Rather, this alleged fifth portion appears to be a physical label moiety. As set forth further below, the combination of Zhang et al. for allegedly describing a solid support or for providing motivation for the substitution of allegedly similar amplification methods fails to cure the above deficiencies. Accordingly, absent a teaching, suggestion or motivation to use a capture probe that specifically hybridizes to an adapter sequence, the claims cannot be obvious over the cited art because the cited combination of references fail to provide the requisite teaching, suggestion or motivation for combining all elements of the claimed invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. According to the definition of "adaptor sequence" (see the specification, page 19, third paragraph), adaptor sequence can be any kind of sequence. Since Barany *et al.,* teach that a first oligonucleotide probe having a target-specific portion, addressable array-specific portion and a upstream primer-specific portion, and a second oligonucleotide probe having a target-specific portion, a downstream primer-specific portion, and a detectable label are hybridized adjacent to one another on a corresponding target nucleotide sequence and are ligated together in a ligase chain reaction, if there is a mismatch in ligation end of the first or second probe, this mismatch will interfere with such ligation. Then unligated the first probe and the second probe are removed and PCR-amplify the ligation product sequence (in the second

probe) wherein one primer has a detectable reporter label. Finally, **PCR products are hybridized with a DNA array by the addressable array-specific portions of the PCR products (from the first oligonucleotide from Barany *et al.*,)** wherein the array has different capture oligonucleotides immobilized at different particular sites and have nucleotide sequences complementary to the addressable array-specific portions of the PCR products, and the labels of the PCR products captured on the DNA array at particular sites are detected (see Figure 60, and column 80, claim 1 in columns 157 and 158), a portion of the addressable array-specific portions from the first oligonucleotide from Barany *et al.,* is considered as the fifth portion comprising an adapter sequence as recited in claims 26, 33, 54, and 58 and does not hybridize to the target sequence and "the claimed ligation probes are distinct from the probes of Barany *et al.,* which hybridize to the target sequence" argued by applicant is incorrect.

II. In page 20, last paragraph bridging to page 21, first paragraph of applicant's remarks, applicant argues that "there has been no showing that the two methods are equivalent, used for the same purpose or expected to achieve their expected results such that one skilled in the art would arrive at the claimed first immobilization step of the target sequence with a second immobilization step for capturing and detection. The Office asserts that the cited references describing equivalent methods that employ a single immobilization step renders the invention obvious. However, the claims recite both a first immobilization step of the target sequences and a second immobilization step for capture of amplicons with an array. Equivalency of one method employing a single immobilization step with another method also employing a single immobilization step would indicate to one skilled in the art that any combination of the two

equivalent methods would also result in method that similarly employs a single immobilization step. The Office has failed to point out in the cited references where the two methods used for the same purpose would teach, suggest or motivate one of ordinary skill in the art to arrive at the claimed first and second immobilization steps. Rather, equivalency of the methods described in the cited art point to the opposite conclusion of maintaining a single immobilization step".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since Barany *et al.,* teach all limitations of independent claims 26, 33, 54, and 58 except providing a support on which the target sequence is immobilized as recited in step a) of independent claims 26, 33, 54, and 58 while claims 26, 33, 54, and 58 do not require that step a) must perform before step b), binding of target nucleic acid-probe complex to streptavidin-coated paramagnetic beads taught by Zhang *et al.,* is considered to provide a support on which the target sequence is immobilized recited in step a) of claims 26, 33, 54, and 58, and both Barany and Zhang *et al.,* teach LDR/PCR method, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 26, 33, 54, and 58 in view of the patents of Barany *et al.,* and Zhang *et al.,* by simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.,*) from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.,*) in order to make hybridization probes (ie., a plurality of amplicons in step f) of claims 26, 33, 54, and 58) during the process for performing the methods recited in claims 26, 34, 54, and 58 since LDR/PCR method of Zhang *et al.,* and LDR/PCR method of Barany *et al.,* are equivalent methods and are used for the same purpose (ie., producing hybridization probes). Therefore,

"there has been no showing that the two methods are equivalent, used for the same purpose or expected to achieve their expected results such that one skilled in the art would arrive at the claimed first immobilization step of the target sequence with a second immobilization step for capturing and detection" argued by applicant is incorrect.

III. In page 21, second paragraph of applicant's remarks, applicant argues that "the Office's apparent reasoning that 'replacement' or 'substitution' of one method for the other is sufficient to sustain an obvious rejection is unsupported by in the references or by the proffered rationale. To arrive at the claimed invention one skilled in the art would be required to modify one method with elements of the other method to arrive at a third, non-equivalent method. Replacement or substitution, without more, fails to teach, suggest or provide the requisite motivation to arrive at the claimed invention because replacement or substitution of one method for another method used for the same purpose would yield the same result - namely, for producing hybridization probes using a single immobilization step (see, for example, Office Action mailed March 23, 2006, at p.9, para.1). The Office has not pointed to any teaching or suggestion that would motivation one of ordinary skill to modify either or both single immobilization methods to generate a new method containing two immobilization steps. The mere assertion that the two methods can be substituted because they are equivalent and used for the same purpose fails to satisfy this requirement under § 103(a)" and "the law is clear with respect to the requirements for properly combining references. Simply identifying elements in the cited art fails to render a claimed invention obvious absent a specific reason to do so. Here, because the methods are

conceded to be equivalent, there can be no specific reason to combine to arrive at a third, and different, method".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the examiner notes that one skilled in the art would be required to modify the method of Barany *et al.,* in order to arrive at the claimed invention. Second, the rejection is based on the replacement of LDR/PCR method of Barany *et al.,* from LDR/PCR method of Zhang *et al.,* in order to provide a support on which the target sequence is immobilized recited in step a) of claims 26, 33, 54, and 58 and is not based on the replacement of all methods of Barany *et al.,* from all method of Zhang *et al.,* as argued by applicant and applicant appears misunderstanding the rejection. Third, the rejection has provided motivation to combine Barany *et al.,* and Zhang *et al.,* (see above rejection).

IV. In page 22, second paragraph bridging to page 23, first paragraph of applicant's remarks, applicant argues that "[T]here is nothing in the cited art or in the equivalency, use for the same purpose, replaceability or substitutability of the methods described in the cited art which provides the motivation to arrive at the claimed invention as a solution to this problem facing the inventor. Both cited references are directed to detection of nucleic acid sequences and describe a specific detection format that includes a single immobilization step. Neither reference provides any indication that inclusion of multiple immobilization steps will provide any advantage or even a desirable result. Rather, both Barany et al. and Zhang et al. describe methods of detection employing a single immobilization step. Therefore, no alternatives are taught or suggested in either Barany et al. or Zhang et al. that include use of a second immobilization step as is claimed

by the invention, whether to provide a flexible assay for accurate determination and quantitation of nucleic acid sequences as taught in the specification or for any other reason. Hence, the Office's conclusion appears to be a hindsight reconstruction focusing on the solution and ignoring the requirement for a teaching, suggestion or motivation for establishing a *prima facie* case of obviousness through a combination of art. The cited combination further appears to be an improper hindsight analysis because there also is no motivation to modif2 one method describing a single immobilization step with another method which also describes a single immobilization step to arrive at two different immobilization steps absent a specific reason to do so. Both Barany et al. and Zhang et al. may, *arguendo*, be considered to be skilled in the art of nucleic acid detection. However, neither reference suggests the possibility of modifying either method to contain two separate immobilization steps. As evident from both Barany et al. and Zhang et al., those which might be considered to be skilled in the art, failed to even contemplate that inclusion of multiple immobilization steps would be beneficial. Neither the Office nor any of the cited references provide any explanation why one of ordinary skill would be motivated to arrive at a method that contains two different immobilization steps. The simple explanation that the two methods are equivalent or substitutable improperly views the problem from the solution as it is claimed by the invention, rather than to view it from the problem facing the inventor at the time of the invention, and constitutes hindsight. Absent any showing that the cited references themselves teach or suggest the claimed invention or, based on the combination of references, absent a particular articulation of why one of ordinary skill in the art would be motivated to arrive at the claimed invention employing a first immobilization step for the targets and a second

immobilization step for the anaplicons, Barany et al. and Zhang et al. fail to render the invention obvious for merely describing certain elements of the claimed invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since Barany *et al.,* teach all limitations of independent claims 26, 33, 54, and 58 except providing a support on which the target sequence is immobilized as recited in step a) of independent claims 26, 33, 54, and 58 while claims 26, 33, 54, and 58 do not require that step a) must perform before step b), binding of target nucleic acid-probe complex to streptavidin-coated paramagnetic beads taught by Zhang *et al.,* is considered to provide a support on which the target sequence is immobilized recited in step a) of claims 26, 33, 54, and 58, and both Barany and Zhang *et al.,* teach LDR/PCR method, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 26, 33, 54, and 58 in view of the patents of Barany *et al.,* and Zhang *et al.,* by simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.,*) from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.,*) in order to make hybridization probes (ie., a plurality of amplicons in step f) of

claims 26, 33, 54, and 58) during the process for performing the methods recited in claims 26, 34, 54, and 58 since LDR/PCR method of Zhang *et al.,* and LDR/PCR method of Barany *et al.,* are equivalent methods and are used for the same purpose (ie., producing hybridization probes). Second, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

6. Claims 11, 12, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (1996) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61, and further in view of Gebeyehu *et al.,* (US Patent No. 4,921,805, published on May 1, 1990).

The teachings of Barany *et al.,* and Zhang *et al.,* have been summarized previously, *supra.*

Barany *et al.,* and Zhang *et al.,* do not disclose that said double-stranded specific moiety is an intercalator attached to a support wherein said support is a bead as recited in claims 11, 12, 43, and 44.

Gebeyehu *et al.,* teach to use an intercalator attached to a bead to separate non-hybridized probes from hybridized probes (see column 3, lines 39-54 and claims 1-10 in columns 12-14).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using methods recited in claims 11, 12, 43, and 44 in view of the prior art of Barany *et al.,* Zhang *et al.,* and Gebeyehu *et al.*. One having ordinary skill in the art would have been motivated to do so because Gebeyehu *et al.,* have successfully separated non-hybridized probes from hybridized probes using an intercalator attached to a bead and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner) from another well known nucleic acid separation method (based on the interaction between a double nucleic acid probe with an intercalator) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the nucleic acid separation method taught by Zhang *et al.,* and the nucleic acid separation method taught by Gebeyehu *et al.,* are equivalent methods and are used for the same purpose (ie., removing non-hybridized probes).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

7. Claims 9, 23, 30, 41, 53, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (1996) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61, and further in view of Seradyn Particle Technology (November 1996, pages 1-7).

The teachings of Barany *et al.,* and Zhang *et al.,* have been summarized previously, *supra.*

Seradyn Particle Technology (page 7) confirms that streptavidin-coated paramagnetic beads taught by Zhang *et al.,* comprise a plastic material as recited in claims 23, 30, 53, and 55 since these beads has polystyrene core.

Barany *et al.,* Zhang *et al.,* and Seradyn Particle Technology do not disclose that the target sequence is labeled with a binding ligand as recited in claims 9 and 41. However, Zhang *et al.,* teach steps b) to d) in claims 9 and 41 except the probe, not the target sequence, is labeled with a binding ligand in step a) (see column 8 and 10-13).

However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using a method recited in claim 9 or 41 in view of the prior art of Barany *et al.,* Zhang *et al.,* and Seradyn Particle Technology. One having ordinary skill in the art would have been motivated to do so

because a method for labeling different nucleic acids with a binding ligand was known in the art at the time the invention was made and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner taught by Zhang *et al.,*) from another well known nucleic acid separation method (based on the interaction between a ligand on a nucleic acid probe with its binding partner) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

8. Claim 37 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (1996) as applied to claims 10, 13, 19-22, 26, 31, 33, 35,

42, 45, 49-52, 54, 56, 58, 59, and 61 above, and further in view of Monforte *et al.,* (US Patent No. 5,830,655, published on November 3, 1998).

The teachings of Barany *et al.,* and Zhang *et al.,* have been summarized previously, *supra.*

Barany *et al.*, and Zhang *et al.,* do not disclose that said target sequence is attached to said support by direct chemical attachment of said target sequence to said support as recited in claims 37 and 63.

Monforte *et al.,* teach to immobilize nucleic acid templates by attachment to a solid support before a primer extension assay. Immobilization is via a covalent or non-covalent linkage (see last paragraph of column 6 and claims 1-3 in column 63).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 37 or 63 by attaching target sequences onto a solid support in view of the patents of Barany *et al.,* Zhang *et al.,* and Monforte *et al.*. One having ordinary skill in the art would have been motivated to do so because Monforte *et al.,* have successfully attached nucleic acid templates to a solid support before amplification of the nucleic acid templates and the immobilization of the nucleic acid templates to a solid support would enhance to separate hybridized complexes formed by the nucleic acid templates and hybridized probes from unhybridized probes and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner that immobilizes on a solid support taught by Zhang *et al.,*) from another well known nucleic acid separation method (based on the

interaction between ligation probes with target sequences immobilized on a solid support) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the nucleic acid separation method taught by Zhang *et al.*, and the nucleic acid separation method taught by Monforte *et al.*, are equivalent methods and are used for the same purpose (ie., removing non-hybridized probes).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

9. Claims 36 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.*, (1997) in view of Zhang *et al.*, (1996) and further in view of Monforte *et al.*, (1998) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 37, 42, 45, 49-52, 54, 56, 58, 59, 61, and 63 above, and further in view of Brown *et al.*, (US Patent No. 5,807,522, published on September 15, 1998).

The teachings of Barany *et al.*, Zhang *et al.*, and Monforte *et al.*, have been summarized previously, *supra.*

Barany *et al.*, Zhang *et al.*, and Monforte *et al.*, do not teach that said target sequence is attached to said support by absorption of said target sequence on said support wherein said support comprises charged groups as recited in claims 36 and 62.

Brown *et al.*, teach to immobilize nucleic acids onto a support comprising charged groups (ie., a slide with a layer of poly-l-lysine) (see column 16).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 36 or 62 by attaching target sequences taught by Zhang *et al.*, onto a solid support comprising charged groups in view of the patents of Barany *et al.*, Monforte *et al.*, and Brown *et al.*. One having ordinary skill in the art would have been motivated to do so because, due to interaction between negative charges of the nucleic acids and positive charges of the support, immobilization of nucleic acids onto a solid support comprising positive charged groups would increase efficiency of the immobilization and the simple replacement of one solid support (ie., the support taught by Monforte *et al.*.) from another solid support (ie., the support with positive charges taught by Brown *et al.*) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since attaching target sequences onto a solid support comprising positive charged groups would enhance absorption of the target sequence on the support due to charge interaction.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

10. Claims 38 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (1997) in view of Zhang *et al.,* (1996) and further in view of Monforte *et al.,* (1998) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 37, 42, 45, 49-52, 54, 56, 58, 59, 61, and 63 above, and further in view of Johnson *et al.,* (US Patent No. 6,372, 813, published on June 25, 1999).

The teachings of Barany *et al.,* Zhang *et al.,* and Monforte *et al.,* have been summarized previously, *supra.*

Barany *et al.*, Zhang *et al.,* and Monforte *et al.,* do not teach that said target sequence is attached to said support by photocrosslinking said target sequence to said support as recited in claim 36.

Johnson *et al.,* teach to photocrosslink a nucleic acid onto a solid support (see example 5, column 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 38 or 64 by attaching target sequences onto a solid support by photocrosslinking in view of the patents of Barany *et al.*, Zhang *et al.*, Monforte *et al.*, and Johnson *et al.*. One having ordinary skill in the art would have been motivated to do so because Johnson *et al..*, have successfully photocrosslinked a nucleic acid onto a solid support and the simple replacement of one well known nucleic acid immobilization method (an immobilization method taught by Monforte *et al.*,) from another well known nucleic acid immobilization method (an immobilization method taught by Johnson *et al.*,) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the nucleic acid immobilization method taught by Monforte *et al.*, and the nucleic acid immobilization method taught by Johnson *et al.*, are equivalent methods and are used for the same purpose (ie., nucleic acid immobilization).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 24 of applicant's remarks, applicant argues that "[A]s set forth above" Barany et al., in view of Zhang et al. do not "provide all elements of the claimed invention or a motivation to combine the respective references. Accordingly, the independent claims are unobvious over the cited combination of references. The above tertiary references are cited allegedly for describing a further element found within the dependent claims. Because the cited art fails to teach, suggest or provide a motivation for each and every element of the claimed invention and because the tertiary references are directed to further elements within the dependent claims, the citations to Gebeyehu et al., Seradyn Particle Technology, Monforte et al. or Johnson et al. cannot cure the deficiencies of the primary and secondary references".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because Barany *et al.,* in view of Zhang *et al.* provide all elements of the claimed invention or a motivation to combine the respective references (see Response to Arguments related to above Rejection Item No. 5).

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

March 29, 2007

FRANK LU
PRIMARY EXAMINER